IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

HORIZON MEDICINES LLC,

Plaintiff,

v.

ALKEM LABORATORIES LTD.,

Defendant.

C.A. No. 1:18-cv-01014-RGA

HORIZON'S ANSWERING POST-TRIAL BRIEF REGARDING VALIDITY

BARNES & THORNBURG LLP
Chad S.C. Stover (No. 4919)
1000 N. West Street, Suite 1500
Wilmington, Delaware 19801
Telephone: (302) 300-3474
chad.stover@btlaw.com

Of Counsel:
Caryn C. Borg-Breen
Jessica Tyrus Mackay
Timothy J. O'Brien
GREEN, GRIFFITH & BORG-BREEN LLP
676 North Michigan Avenue, Suite 3900
Chicago, Illinois 60611
Telephone: (312) 883-8000
cborg-breen@greengriffith.com
jmackay@greengriffith.com
tobrien@greengriffith.com

Attorneys for Plaintiff Horizon Medicines LLC

Dated: October 6, 2020

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

Other Authorities

TABLE OF CITED EXHIBITS

Exhibit No.	Identified As	Description
DTX 110		Horizon Therapeutics HZT-501: Phase 3 Clinical Study, Background Information, "GI Friendly NSAID for Mild to Moderate Pain Relief"
DTX 114	"Singh"	Gurkirpal Singh, *Recent Considerations in Nonsteroidal Anti-Inflammatory Drug Gastropathy*, 105 AM. J. MED. 31S (1998)
DTX 120		Pepcid® Package Insert (June 6, 2002)
DTX 121		Horizon Therapeutics Company Update Slide Deck
DTX 136	"'671 publication"	U.S. Patent Application Publication No. 2005/0020671 A1
DTX 281		Motrin® Ibuprofen Tablets (800 mg) Package Insert (Revised January 2006)
DTX 749	"Edge"	D P Edge, *High Dose Famotidine in Ranitidine Resistant Severe Oesophagitis: A Pilot Study*, 103 N.Z. MED. J. 150 (1990)
DTX 772	"Echizen"	Hirotoshi Echizen & Takashi Ishizaki, *Clinical Pharmacokinetics of Famotidine*, 21 CLINICAL PHARMACOKINETICS 178 (1991)
DTX 785	"'876 publication"	U.S. Patent Application Publication No. 2005/0281876 A1
DTX 928		Melissa Rich & James M. Scheiman, *Nonsteroidal Anti-Inflammatory Drug Gastropathy at the New Millennium: Mechanisms and Prevention*, 30 SEMINARS ARTHRITIS & RHEUMATISM 167 (2000)
DTX 989		Lynda S. Welage, *Pharmacological Properties of Proton Pump Inhibitors*, 23 PHARMACOTHERAPY 74S (2003)
PTX 1	"'033 patent"	Certified copy of U.S. Patent No. 8,067,033
PTX 7-B		Nwokolo, et al., "Tolerance during 29 days of conventional dosing with cimetidine, nizatidine, famotidine or ranitidine," Aliment Pharmacol. Therap. (1990) 4 (Suppl. 1) 29-45
PTX 262	"Taha"	Ali S. Taha et al., *Famotidine for the Prevention of Gastric and Duodenal Ulcers Caused by Nonsteroidal Antiinflammatory Drugs*, 334 NEW ENG. J. MED. 1435 (May 30, 1996)
PTX 277		UPM Pharmaceuticals to Horizon regarding development of combination tablet
PTX 322		Curriculum Vitae of James M. Scheiman, M.D.

Exhibit No.	Identified As	Description
PTX 371	"'096 publication"	U.S. Patent Application Publication No. 2007/0043096 Al
PTX 376	"'696 patent"	U.S. Patent No. 5,593,696
PTX 442	"Junnarkar"	Gunjan H. Junnarkar & Salomon Stavchansky, *Isothermal and Nonisothermal Decomposition of Famotidine in Aqueous Solution*, 12 PHARMACEUTICAL RES. 599 (1995)
PTX 492	"Rostom"	A. Rostom et al., *Prevention of NSAID-induced Gastroduodenal Ulcers*, COCHRANE DATABASE SYSTEMATIC REVS. (John Wiley & Sons, Ltd. 2002, rev. 2011), https://www.cochranelibrary.com /cdsr/doi/10.1002/14651858.CD002296/epdf/full
PTX 496		James M. Scheiman & A. Mark Fendrick, *Practical Approaches to Minimizing Gastrointestinal and Cardiovascular Safety Concerns with COX-2 Inhibitors and NSAIDs*, 7 ARTHRITIS RESEARCH & THERAPY S23 (2005)
PTX 500		Scheiman, et al., "Compliance with GERD Therapy: Nonsteroidal Anti-Inflammatory Drugs, Aspirin, and Gastrointestinal Prophylaxis: An Ounce of Prevention" Reviews in Gastroenterological Disorders, Vol. 5, Supp 2, 539-549 (2005)
PTX 531	"Wolfe"	Wolfe, et al., "Gastrointestinal Toxicity of Nonsteroidal Anti-inflammatory Drugs," 340 NEW ENG. J. MEDICINE 1888
PTX 535	"Yanagisawa"	Isao Yanagisawa et al., *Studies on Histamine H2 Receptor Antagonists. 2. Synthesis and Pharmacological Activities of N-Sulfamoyl and N-Sulfonyl Amidine Derivatives*, 30 J. MEDICINAL CHEMISTRY 1787 (1987)
PTX 559	"USP NF" or "USP"	THE UNITED STATES PHARMACOPEIA: NATIONAL FORMULARY (29th ed. 2006)
PTX 580		NEXIUM® Prescribing Information (October 11, 2006 Label obtained from Drugs@FDA website (https://www.accessdata.fda.gov/scripts/cder/daf/))
PTX 584		Prevacid® Prescribing Information (Rev. Sept. 2006)
PTX 672		January 31, 2006 Formulation Development and Manufacture of Clinical Batches of Ibuprofen/Famotidine Combination Tablet and Soft Gelatin Capsule
PTX 707-A		Excerpt from FDA IND. No. 72,116 Correspondence

Exhibit No.	Identified As	Description
PTX 707-B		Excerpt from FDA IND. No. 72,116 Correspondence
PTX 763		"Fixed Dose Combination Product of ibuprofen and famotidine for Pain Relief," Pre-IND Meeting Background Information
PTX 766		"Ibuprofen/famotidine Combination Product for Pain Relief," Request for Pre-IND Meeting
PTX 771		IND 72,116; SN 0000, Section 7 Chemistry, Manufacturing, and Controls

Horizon Medicines LLC ("Horizon") respectfully submits its answering validity post-trial brief in response to Alkem Laboratories Ltd.'s ("Alkem") September 26, 2020 opening post-trial brief (D.I. 218, "Alk. Op. Br.") pursuant to the Court's Scheduling Order (D.I. 209).

I. INTRODUCTION

The '033 patent is presumed valid. *See Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 97 (2011). Therefore, to prevail, Alkem must prove by clear and convincing evidence, *id.*, that each of the Asserted Claims (i.e., claims 1, 8, 11, and 14) of U.S. Patent No. 8,067,033 (PTX 1, the "'033 patent") are invalid due to obviousness or indefiniteness. Alkem cannot do so here.

The Asserted Claims of the '033 patent reflect two important discoveries—an inventive dosing regimen of 26.6 mg famotidine and 800 mg ibuprofen given three times per day ("TID") for reducing the risk of ibuprofen-induced ulcers, and an inventive stable composition containing ibuprofen and famotidine, two highly incompatible drugs. Both of Alkem's obviousness combinations include the '096 publication (PTX 371). However, as set forth in Section II.A, the '096 publication is not available as prior art to the '033 patent because it is not the work of "another"—which makes sense given that the '033 patent and the '096 publication were filed as part of the same research and development program. Thus, as discussed in Section II.B, Alkem cannot set forth a *prima facie* case of obviousness because no other reference discloses 26.6 mg famotidine and 800 mg ibuprofen given TID.

Additionally, Alkem's obviousness case fails because a person of ordinary skill in the art ("POSA") would not have been motivated to pursue the claimed invention with any reasonable expectation of success. A POSA would not have expected that 26.6 mg famotidine, an H_2-receptor antagonist, would be effective for reducing ibuprofen-induced ulcers (*see* Sections II.C.1-2), or that 800 mg ibuprofen could be formulated with 26.6 mg famotidine in a single unit dosage form that meets the high degree of stability set forth in the Asserted Claims (*see* Sections

II.C.3-4). Finally, as set forth in Section III, Alkem's arguments that the claim term "sulfamide" is indefinite are belied by the evidence, including testimony from Alkem's own expert, Dr. Laird.

II. THE ASSERTED CLAIMS OF THE '033 PATENT ARE NOT OBVIOUS

A. The '096 publication is not available as prior art to the '033 patent under 35 U.S.C. § 102(a)

Alkem asserts that the Asserted Claims of the '033 patent are invalid as obvious over the '096 publication in light of its disclosure of a composition comprising 800 mg ibuprofen and 26.6 mg famotidine that is allegedly suitable "for use according to a TID (three times per day) administration schedule" "for reducing the risk of developing ibuprofen-induced ulceration in a human patient requiring ibuprofen for an ibuprofen-responsive condition" and further allegedly having the release profile recited in dependent claim 11 of the '033 patent. (Alk. Op. Br. at 9, 22-23, 25-26, 28-29; Tr. (Chambliss Dir.) at 480:4-481:8, 485:10-488:11, 503:20-504:17, 506:9-507:9.) Alkem asserts that the '096 publication is prior art pursuant to 35 U.S.C. § 102(a). (Alk. Op. Br. at 9.) Alkem is wrong.

The '096 publication cannot be used as prior art to the '033 patent because the subject matter of the '096 publication is not the work of "another" as required by 35 U.S.C. § 102(a). The fact that the inventive entities identified on the face of the '096 publication (Dr. George Tidmarsh, Barry Golombik, and Tianshiuan Lii) and the '033 patent (Tidmarsh and Jerry Xu) are different (Tr. (Tidmarsh Dir.) at 110:11-14, 122:1-4; Tr. (Tidmarsh Cr.) at 178:4-10; PTX 1 at p. 2; PTX 371 at p. 1)[1] is not dispositive.[2] What matters is that the same inventive entity (i.e., either

[1] Citations to exhibit pages ("p." or "pp.") refer to the page numbers affixed by the parties as "PTX0XXX_0**XXX**" or "DTX0XXX_000**XXX**."

[2] The '033 patent and the '096 publication also share the same assignee, Horizon, and the '033 patent incorporates by reference Patent Application No. 11/489,275, the application underlying the '096 publication. (PTX 1 at p. 2, 11:55-56; PTX 371 at p. 1.) *See Ethicon Endo-Surgery, Inc.*

Tidmarsh with Golombik, or Tidmarsh alone) invented the overlapping subject matter.

1. Legal standards

To qualify as prior art under 35 U.S.C. § 102(a) (pre-AIA), the subject matter relied upon in a prior publication must have been conceived by "another," meaning by a different inventive entity. *Riverwood Int'l Corp. v. R.A. Jones & Co.*, 324 F.3d 1346, 1356 (Fed. Cir. 2003) ("What is significant is not merely the differences in the listed inventors, but whether the portions of the reference relied on as prior art, and the subject matter of the claims in question, represent the work of a common inventive entity."); *see also Ethicon Endo-Surgery*, 689 F. Supp. 2d at 942 (the inquiry is "what claims or elements of the [prior art patents] were invented by [the overlapping inventors] and which claims or elements of the [patents-in-suit] were also invented by them," where "[o]nly [the overlapping] claims or elements … would not be prior art."). The '096 publication cannot be "the work of another" because "[d]isclosure to the public of one's own work constitutes a bar to the grant of a patent claiming the subject matter so disclosed (or subject matter obvious therefrom) ***only*** . . . when the disclosure creates a one-year time bar … under [35 U.S.C. §] 102(b)."[3] *In re Katz*, 687 F.2d 450, 454 (C.C.P.A. 1982) (emphasis added); *see also* MPEP § 2132.01 (pre-AIA). This is consistent with the flexible standard for collaborative research and development and "the liberalization of the requirements for filing a U.S. application as joint inventors wrought by the 1984 amendment of 35 U.S.C. § 116," "which permits inventors who work together to file jointly for a single patent." *Abbott GMBH & Co.,*

v. Hologic, Inc., 689 F. Supp. 2d 929, 942 (S.D. Ohio 2010) (recognizing the asserted patent and prior art were related in "by another" context).

[3] The '096 publication cannot be 35 U.S.C. § 102(b) prior art because the '033 patent is entitled to its provisional priority date, which Alkem has never disputed. (Tr. (Tidmarsh Dir.) at 46:10-47:13; Tr. (Chambliss Dir.) at 442:25-443:4; Tr. (Chambliss Cr.) at 541:16-542:1; PTX 1 at p. 2; PTX 18 at p. 3; *compare* PTX 1 at pp. 5-12 *with* PTX 18 at pp. 6-27.)

KG v. Centocor Ortho Biotech, Inc., 870 F. Supp. 2d 206, 241-42 (D. Mass. 2012).

"Conception is the touchstone to determining inventorship." *Fina Oil & Chem. Co. v. Ewen*, 123 F.3d 1466, 1473 (Fed. Cir. 1997). There is no "explicit lower limit on the quantum or quality of inventive contribution required for a person to qualify as a joint inventor" so long as they contributed "to the conception of the claimed invention." *Vanderbilt University v. ICOS Corp.*, 601 F.3d 1297, 1301 (Fed. Cir. 2010). The level of contribution may be as low as suggesting a "low dose" of a known drug. *See Ferring B.V. v. Allergan, Inc.*, 166 F. Supp. 3d 415, 424-26 (S.D.N.Y. 2016).

"The determination of whether a person is a joint inventor is fact specific, and no bright-line standard will suffice in every case." *Fina Oil & Chem.*, 123 F.3d at 1473. Conception must typically be corroborated, preferably by contemporaneous disclosure, *Ferring B.V.*, 166 F. Supp. 3d at 421, but the Federal Circuit has recognized in the context of determining whether prior art was by "another" that contemporaneous documentary evidence is not always required, and that "[a] number of factors may guide the corroboration assessment," such that "it is an evaluation of all pertinent evidence that must be made so that a sound determination of the credibility of the inventor's story may be reached. … In certain cases, we have recognized that even non-documentary, circumstantial evidence may sufficiently corroborate." *EmeraChem Holdings, LLC v. Volkswagen Grp. of Am., Inc.*, 859 F.3d 1341, 1347 (Fed. Cir. 2017) (alterations and internal quotations omitted); *see also In re Katz*, 687 F.2d at 455 (finding inventor's declaration that prior work was not by "another" alone sufficient to overcome 35 U.S.C. § 102(a) rejection).

Alkem bears the burden of persuasion by clear and convincing evidence that the '096 publication is the work of "another." *See United Video Properties, Inc. v. Haier Grp. Corp.*, No. CV 11-1140 (KAJ), 2014 WL 12774922, at *4, *30 (D. Del. May 16, 2014); *see generally Sandt*

Tech., Ltd. v. Resco Metal & Plastics Corp., 264 F.3d 1344, 1350 (Fed. Cir. 2001) ("The presumption of validity . . . requires those challenging validity to introduce clear and convincing evidence on all issues relating to the status of a particular reference as prior art.").

2. The overlapping subject matter was invented by either Tidmarsh with Golombik or Tidmarsh alone

In this case, the evidence clearly shows that the idea of a combination dosage form comprising 800 mg ibuprofen and 26.6 mg famotidine for three times a day administration to reduce the risk of developing ibuprofen-induced ulceration in a human patient requiring ibuprofen for an ibuprofen-responsive condition was conceived of by Tidmarsh, either alone or with Golombik. The evidence shows that neither Lii nor Xu contributed, and could not have contributed, to the conception of this subject matter.

Tidmarsh and Golombik founded Horizon Therapeutics in 2004 after learning that the widely prescribed COX-2 inhibitor, VIOXX®, was being pulled from the market due to safety concerns. (Tr. (Tidmarsh Dir.) at 47:23-48:18; Tr. (Golombik Dir.) at 225:1-17.) They believed that physicians would revert to prescribing non-selective NSAIDs, which were associated with GI toxicity, and they formed Horizon to create a safer NSAID by combining an NSAID with a gastroprotectant. (Tr. (Tidmarsh Dir.) at 47:23-48:18, 49:9-21; Tr. (Golombik Dir.) at 225:1-17.)

Although Tidmarsh was a medical doctor and a scientist and Golombik had only a background in business, Tidmarsh and Golombik worked together using an iterative process whereby they debated different NSAID and gastroprotectant choices and different dosing regimens, to come up with the idea for an immediate release, combination pharmaceutical composition containing 800 mg ibuprofen and 26.6 mg famotidine, dosed according to a TID administration schedule to reduce the risk of developing ibuprofen-induced ulcers. (Tr. (Tidmarsh Dir.) at 112:12-113:20, 114:2-115:2, 115:25-116:7, 117:6-118:14; Tr. (Golombik

Dir.) at 225:18-228:7, 228:19-230:14, 232:9-20, 233:2-14, 234:10-24, 235:8-23.) Tidmarsh and Golombik each testified that they are not aware of anyone else contributing to idea of a combination dosage form comprising 800 mg ibuprofen and 26.6 mg famotidine for three times a day administration to reduce the risk of developing ibuprofen-induced ulceration in a human patient requiring ibuprofen for an ibuprofen-responsive condition. (Tr. (Tidmarsh Dir.) at 116:19-25; Tr. (Golombik Dir.) at 232:1-8.)

Neither Lii, a named inventor on the ’096 publication but not on the ’033 patent, nor Xu, a named inventor on the ’033 patent but not on the ’096 publication, contributed to the overlapping subject matter. Lii was a formulation chemist with UPM, a contract research laboratory retained by Horizon, and Xu was a formulation scientist with Pii, another contract research laboratory retained by Horizon. (Tr. (Tidmarsh Dir.) at 53:2-5, 82:3-9, 88:13-15, 110:11-14; Tr. (Golombik Dir.) at 233:16-22, 241:24-242:3.) Horizon retained both UPM and Pii to prepare formulations of its proposed combination ibuprofen and famotidine drug product. (Tr. (Tidmarsh Dir.) at 53:2-5, 81:25-82:9; Tr. (Golombik Dir.) at 241:24-242:3; PTX 277 at p. 1; PTX 672 at p. 1.) Horizon engaged UPM on April 19, 2005, to prepare immediate release tablets containing 400 mg ibuprofen and 10 mg famotidine. (Tr. (Tidmarsh Dir.) at 77:25-78:24; PTX 277 at pp. 1, 3). Horizon engaged Pii on February 2, 2006, to prepare immediate release tablets containing 800 mg ibuprofen and 26.6 mg famotidine. (Tr. (Tidmarsh Dir.) at 82:3-83:19; PTX 672 at pp. 1, 4, 23).

By the time Horizon retained UPM and later Pii, Tidmarsh and Golombik had already conceived of a combination dosage form comprising 800 mg ibuprofen and 20 or 26.6 mg famotidine for TID administration to reduce the risk of developing ibuprofen-induced ulceration in a human patient requiring ibuprofen for an ibuprofen-responsive condition. (Tr. (Tidmarsh

Dir.) at 78:2-24, 125:19-127:15, 128:16-129:2; Tr. (Golombik Dir.) at 245:6-11.) This is corroborated by Horizon's March 22, 2005, pre-IND Meeting Request to the FDA, which was prepared by both Tidmarsh and Golombik (Tr. (Tidmarsh Dir.) at 51:7-52:22; PTX 766 at pp. 1, 3-5), as well as Horizon's May 9, 2005, Background Information submitted to the FDA in advance of a Pre-IND Meeting (Tr. (Tidmarsh Dir.) at 54:16-57:2; PTX 763 at pp. 1, 3-4), and Horizon's January 24, 2006, original IND submission to the FDA (Tr. (Tidmarsh Dir.) at 63:1-66:16; PTX 768 at p. 1; PTX 771 at p. 3.) Further, as early as March 2005, Dr. Tidmarsh and Mr. Golombik had determined that the combination drug product would be dosed three times per day. (Tr. (Tidmarsh Dir.) at 53:17-20.)

Tidmarsh and Golombik testified that neither Lii nor Xu contributed to the identification of 800 mg ibuprofen and 26.6 mg famotidine, their administration TID, that the combination product would be formulated for immediate release, or that the combination product could be used to reduce the incidence of developing ibuprofen-induced ulcers. (Tr. (Tidmarsh Dir.) at 120:16-121:25, 125:19-127:15, 128:16-129:2; Tr. (Golombik Dir.) at 233:23-234:8, 235:24-236:14.) Tidmarsh testified that Lii was named as a co-inventor of the '096 publication because of his contribution to the identification of formulations, excipients, and methods of manufacture for the admixture formulations disclosed in the publication. (Tr. (Tidmarsh Dir.) at 89:13-20, 127:16-128:15.) Similarly, Tidmarsh testified that Xu was named as a co-inventor on the '033 patent because of his contribution to the disclosed excipients as well as the process for manufacturing the tablets disclosed in the '033 patent. (Tr. (Tidmarsh Dir.) at 118:16-23.) Thus, neither Lii nor Xu contributed to the overlapping subject matter of the '096 publication and the '033 patent, though each was properly named as a co-inventor on the '096 publication and the '033 patent, respectively.

3. The overlapping subject matter is not the work of "another"

Alkem cannot meet its burden by clear and convincing evidence of showing that the overlapping subject matter of the '096 publication is by "another." *United Video*, 2014 WL 12774922, at *4, *30; *Sandt Tech.*, 264 F.3d at 1350.

As Alkem acknowledges (Alk. Op. Br. at 2), the fact that the '096 publication and the '033 patent name different inventors is not dispositive, as "the district court must look beyond the superficial fact that the references were issued to different inventive entities." *See Riverwood*, 324 F.3d at 1356; *Ethicon*, 689 F. Supp. 2d at 942; *see also Abbott GMBH & Co., KG*, 870 F. Supp. 2d at 242 ("[e]ven though an application and a patent have been conceived by different inventive entities, if they share one or more persons as joint inventors, the . . . exclusion for a patent granted to 'another' is not necessarily satisfied"). In this case, the evidence shows that Tidmarsh, either alone or in combination with Golombik (and not Lii or Xu) conceived of a combination product containing 800 mg ibuprofen and 26.6 mg famotidine, dosed TID for reducing the risk of developing ibuprofen-induced ulceration in a human patient requiring ibuprofen for an ibuprofen-responsive condition without any contribution by Lii or Xu. The conception of this overlapping subject matter is the same, regardless of whether such subject matter is set forth in the '096 publication or in the claims of the '033 patent.

Thus, there are two possible scenarios, and under neither one can Alkem establish that the cited disclosures of the '096 publication were invented "by another." The first scenario is that Tidmarsh alone conceived of the overlapping subject matter, because Golombik's contributions do not rise to the level of conception, and accordingly the '033 patent is not the work of "another." If this is the finding of the Court, then no change in inventorship is needed, as Golombik is not listed as an inventor of the '033 patent, and the '096 publication is only a patent publication, not a granted patent. The second scenario is that Tidmarsh and Golombik together

conceived of the overlapping subject matter, in which case Golombik should have been named as a co-inventor on the '033 patent, and the '033 patent also is not the work of "another." If this is the finding of the Court, then Horizon respectfully requests that the Court reconsider its denial of Horizon's request to change the inventorship of the '033 patent pursuant to 35 U.S.C. § 256. The Federal Circuit recognizes that Section 256 is to be interpreted broadly to protect the public interest of assuring correct inventorship designations, and all parties have been properly heard on this issue. *See, e.g.*, *Chou v. Univ. of Chi.*, 254 F.3d 1347, 1358 (Fed. Cir. 2001); *MCV, Inc. v. King-Seeley Thermos Co.*, 870 F.2d 1568, 1570 (Fed. Cir. 1989); *see also Polyzen, Inc. v. RadiaDyne, L.L.C.*, No. 5:11-CV-662-D, 2012 WL 4049841, at *5 (E.D.N.C. Aug. 31, 2012).

B. Alkem cannot set forth a *prima facie* case of obviousness without the '096 publication as prior art

The only reference Alkem cites that discloses a dose of 800 mg ibuprofen or 26.6 mg famotidine for use according to a TID administration schedule is the '096 publication.[4] Because the '096 publication is not available as prior art, for the reasons discussed above, Alkem cannot make out a *prima facie* case of obviousness because no other cited reference discloses the claimed dose and dosing schedule for ibuprofen. This is fatal to Alkem's obviousness case. *See Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011) ("Obviousness requires … [a] showing that the prior art includes separate references covering each separate limitation").

Alkem argues that a POSA would simply "know[] that a standard dose of ibuprofen for treating OA and RA patients was 800 mg TID" (Alk. Op. Br. at 13) or "[understand] that famotidine could be administered TID" (Alk. Op. Br. at 16). However, Alkem must "rely on

[4] Alkem does not—and, indeed, cannot—allege that the USP NF, the '671 publication, or the '876 publication discloses 800 mg ibuprofen or 26.6 mg famotidine dosed TID. (Alk. Op. Br. at 22-23, 25-26; Tr. (Chambliss Cr.) at 542:2-17, 549:19-550:7, 554:12-557:6; Tr. (Little Dir.) 752:22-753:19, 763:4-21, 766:10-767:5, 772:10-18, 777:22-778:2.)

another prior art reference to provide the missing limitation from [the asserted claim]," rather than "on what it considers to be the knowledge of one of ordinary skill in the art." *Advanced Med. Optics, Inc. v. Alcon, Inc.*, 361 F. Supp. 2d 404, 417 (D. Del. 2005).

Alkem cites to Taha (PTX 262), but this reference does not disclose 800 mg ibuprofen or 26.6 mg famotidine TID. While Taha discloses that the patients took "standard doses of an NSAID" (PTX 262 at p. 1), neither Taha nor the art more generally defines such "standard doses." Even assuming that "standard doses" refers to the NSAIDs' FDA-approved "suggested dosages" for treating rheumatoid arthritis and osteoarthritis, the approved dosages for ibuprofen ranged from "1200 mg-3200 mg daily," administered using a variety of unit dosages strengths and dosing intervals. (Tr. (Barnett Dir.) at 583:1-9; Tr. (Barnett Cr.) at 612:2-614:6; Tr. (Scheiman Dir.) at 726:6-24; DTX 281 at p. 11; *see* Alk. Op. Br. at 4.) Indeed, Dr. Gibofsky, the only rheumatologist to testify in this case, treats the majority of his patients with 600 mg ibuprofen TID (1800 mg total daily), consistent with the standard recommended practice of using the "lowest effective dose" of ibuprofen. (Tr. (Gibofsky Dir.) at 210:2-13; Tr. (Barnett Dir.) at 613:4-614:6; DTX 281 at pp. 2, 6.) Thus, the evidence makes clear that "standard doses" can mean different things to different clinicians, clinical study investigators, drug formulators, etc. (Tr. (Scheiman Dir.) at 726:6-20; PTX 262 at p. 1.)

Alkem's only support for Taha disclosing 800 mg ibuprofen or 26.6 mg famotidine TID is the unsupported, conclusory testimony of Dr. Barnett (Alk. Op. Br. at 13; Tr. (Barnett Dir.) at 583:1-14, 607:2-9). But Dr. Barnett is a gastroenterologist, not a rheumatologist, and so he does not regularly treat osteoarthritis or rheumatoid arthritis patients, and his research interests do not involve ibuprofen clinical trial design, arthritic conditions, NSAID gastropathy, gastric or duodenal ulceration, or use of gastroprotectants. (Tr. (Barnett Cr.) at 609:11-611:15, 634:24-

635:12.) Accordingly, Alkem's attempt to read this disclosure into Taha in support of its *prima facie* obviousness case is plainly improper.

C. A POSA would not have been motivated to pursue the claimed invention with any reasonable expectation of success

Alkem cannot meet its burden of showing that a POSA would have been motivated, in the absence of hindsight, to select 800 mg ibuprofen and 26.6 mg famotidine, dosed TID, or would have had any reasonable expectation of success in arriving at a dosage form that would reduce the risk of ibuprofen-induced ulceration or achieve the level of stability required by the Asserted Claims. *See Unigene*, 655 F.3d at 1360; *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008) ("We must . . . be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention."); *see also Novartis Pharm. Corp. v. W.-Ward Pharm. Int'l Ltd.*, 287 F. Supp. 3d 505, 516 (D. Del. 2017) (Andrews, J.) (finding lack of motivation to select a particular drug compound based on "hindsight" bias in overlooking alternative options).

1. A POSA would not have been motivated to use, or had any reasonable expectation of success in using, the H_2RA famotidine for reducing the risk of ibuprofen-induced ulceration

The evidence shows that in 2007, a POSA would *not* have expected famotidine, an H_2-receptor antagonist ("H_2RA") to be efficacious for reducing the risk of ibuprofen-induced ulceration. Accordingly, a POSA seeking to reduce the risk of ibuprofen-induced ulceration would not have been motivated to combine famotidine with ibuprofen, but instead would have utilized a proton pump inhibitor. (Tr. (Scheiman Dir.) at 701:3-16, 739:9-740:22.)

a) A POSA's knowledge of NSAID-induced GI issues in 2007

By 2007, it was well-known that NSAIDs, including ibuprofen, were associated with

serious GI adverse events, including ulceration, perforation, and bleeding of the stomach and/or duodenum (i.e., the upper part of the small intestine), as well as less serious "nuisance" or "dyspeptic" conditions, such as nausea, gastric pain, or heartburn. (Tr. (Scheiman Dir.) at 703:9-19, 705:4-707:8; DTX 281 at pp. 1, 3-4, 9-10.) While these serious conditions were known to be less common than the "nuisance" conditions, it was long understood that these serious adverse events were associated with substantial morbidity due to the significant number of patients taking NSAIDs. (Tr. (Barnett Cr.) at 634:3-5; Tr. (Scheiman Dir.) at 703:9-19, 706:14-707:8; DTX 281 at pp. 9-10; *see also* DTX 114 at p. 1; PTX 531 at p. 2; PTX 496 at p. 1.) These risks were understood to be particularly high for at-risk patients, e.g., elderly patients, patients with previous ulceration, patients taking aspirin or corticosteroids, and/or patients taking chronic or high NSAID doses—i.e., many of the same populations of patients as those taking NSAIDs to treat arthritic conditions. (Tr. (Tidmarsh Dir.) at 52:12-19, 55:8-24; PTX 763 at p. 3; Tr. (Scheiman Dir.) at 705:23-706:13; DTX 281 at pp. 1, 4.)

Also by 2007, the mechanisms by which NSAIDs, including ibuprofen, injure the GI tract were understood to include both (1) local effects, whereby NSAIDs may cross the GI mucosal protective barrier and cause direct chemical harm, and (2) systemic effects, whereby NSAIDs circulating in the blood stream inhibit the synthesis of prostaglandins, i.e., the GI protective mucosal barrier. (Tr. (Scheiman Dir.) at 708:12-709:8; PTX 531 at pp. 4-6.) A stomach (i.e., gastric) or duodenal "ulcer" (i.e., a break in the GI mucosal barrier) exposes the lining of the GI tract to harmful stomach acid, which is present in very large quantities in the stomach and to a lesser extent in the duodenum, thereby potentially leading to perforation and/or life-threatening GI bleeding. (Tr. (Scheiman Dir.) at 707:9-21.) While NSAIDs, including ibuprofen, are associated with both stomach and duodenal ulcers, it was understood prior to 2007 that duodenal

ulcers were easier to treat than gastric ulcers due to differences in the quantities of gastric acid present and other natural protective mechanisms in the duodenum. (Tr. (Scheiman Dir.) at 709:9-24.) It was also understood that the *amount* of stomach acid present was more determinative of the propensity for GI injury than the pH of the stomach, such that a POSA would not have been able to target any specific stomach pH level for reducing the risk of NSAID-induced injury. (Tr. (Scheiman Dir.) at 709:25-710:10.)

In 2007, it was also well-known that *H. pylori* infection was a separate significant cause of gastric and duodenal ulcers, which were known to be easier to treat and maintain than NSAID-induced ulcers, given the aforementioned complex mechanisms of NSAID-induced injury. (Tr. (Barnett Cr.) at 627:16-21; Tr. (Scheiman Dir.) at 714:17-24, 729:21-731:13; DTX 925 at p. 5 ("In the absence of NSAID use, *H. pylori* is accepted as the cause of most ulcers" and "[t]he pathophysiologic mechanisms of NSAID-associated and *H. pylori*-associated ulcers are distinct[.]"); *see also* DTX 114 at p. 5 (describing *H. pylori* ulcers as primarily duodenal).) POSAs therefore understood that any study regarding the prevention of NSAID-induced ulcers would need to exclude patients infected with *H. pylori* (or any other alternative significant risk of ulceration), so as not to obtain falsely positive results based on the prevention of ulcers from sources other than NSAIDs. (Tr. (Scheiman Dir.) at 714:2-24.)

In the years preceding 2007, the recommended treatment for reducing the risk of GI injury in patients taking traditional NSAIDs was to co-administer: (1) a proton pump inhibitor ("PPI")—a class of gastroprotectants which, like H_2RAs, suppress gastric acid; or (2) misoprostol—a synthetic prostaglandin mucosal protectant. (Tr. (Scheiman Dir.) at 710:21-711:17, 712:8-16, 712:20-713:4; Tr. (Scheiman Cr.) at 750:7-8; PTX 531 at p. 10 ("Prophylactic therapy"); *see also* PTX 496 at p. 3.) By 2007, both of these therapies were approved by the

FDA for reducing the risk of NSAID-associated ulcers. (Tr. (Scheiman Dir.) at 703:9-704:4, 712:17-19; 713:5-716:1; PTX 580 at pp. 13-14 (NEXIUM® (esomeprazole, a PPI)); PTX 584 at pp. 19-20 (PREVACID® (lansoprazole, a PPI)); Tr. (Barnett Cr.) at 633:21-634:2.)

b) A POSA would have selected a PPI, not an H_2RA, for reducing the risk of NSAID-induced ulceration in 2007

In the years preceding 2007, H_2RAs were *not* recommended for reducing the risk of NSAID-induced GI injury, and *no* H_2RA had ever been approved by the FDA for this purpose. (Tr. (Scheiman Dir.) at 710:21-712:7, 716:2-4; PTX 531 at 10 (compare recommendations for "Prophylactic therapy," i.e., during concomitant NSAID use, versus treatments for "Dyspepsia" and "Active gastroduodenal ulcer NSAID discontinued"); *see also* PTX 496 at p. 3.) A POSA would have understood that, with regard to famotidine's indications relating to gastric and duodenal ulcers (i.e., putting aside the treatment of gastroesophageal reflux disease and rare hypersecretory conditions), the H_2RA famotidine was only approved by the FDA for healing of *active* ulcers and *maintenance therapy* of healed ulcers—neither of which relates to preventing *NSAID*-induced ulcers. (Tr. (Scheiman Dir.) at 716:5-717:21 (regarding a POSA's understanding that "maintenance therapy" was essentially a management of *H. pylori* ulceration); Tr. (Barnett Cr.) at 614:9-617:1, 617:22-618:10, 620:1-4; DTX 120 at p. 5.) Indeed, a POSA would have understood prevention of *NSAID-induced* ulcers to be much more complicated than treatment or prevention of ulcers generally (*see* Section II.C.1.a, *supra.*, regarding the dual mechanisms of NSAID-induced GI injury; Tr. (Scheiman Dir.) at 708:12-710:10, 714:2-24, 716:5-717:21), a distinction which Alkem overlooks (*see*, *e.g.*, Alk. Op. Br. at 5, 15-16).

While some physicians may have co-prescribed H_2RAs with NSAIDs prior to 2007, that practice was uncommon and for treating "nuisance" symptoms—*not* for reducing the risk of ulceration. (Tr. (Scheiman Dir.) at 717:25-718:8; Tr. (Tidmarsh Dir.) at 59:9-21; PTX 763 at p. 4

("it is not common for patients, especially those at risk, to be treated with gastric acid suppressive therapy during NSAID therapy"); *see also* PTX 531 at 10 (regarding the "empirical" use of H_2RAs for "Dyspepsia").) Dr. Gibofsky testified that, prior to 2007: he only prescribed gastroprotectants, including famotidine, to his arthritic patients taking NSAIDs to "minimize or eliminate" "functional gastric complaints," such as "nausea, dyspepsia, abdominal discomfort, bloating, [or] vomiting," rather than to manage serious adverse events such as ulceration; he did not understand famotidine to be effective to prevent ibuprofen-induced ulcers; and he never prescribed a high daily dose of 80 mg of famotidine. (Tr. (Gibofsky Dir.) at 190:3-20, 213:18-214:19; Tr. (Gibofsky Cr.) at 220:21-221:4.)

Further, the evidence shows that in 2007, a POSA would have chosen a PPI, rather than an H_2RA, to reduce the risk of ibuprofen-induced ulceration because PPIs had (1) better potency, (2) reduced risk of developing tolerance, and (3) reduced risk of mere symptom masking.

Potency: In 2007, H_2RAs were known to be less potent in suppressing gastric acid than PPIs, such that H_2RAs were infrequently prescribed *for any purpose*. (Tr. (Scheiman Dir.) at 698:5-12, 720:8-21; DTX 989 at p. 1 ("Because they are more effective than [H_2RAs], they have largely supplanted H_2RAs for treatment of acid-related diseases, particularly persistent or severe disease"); Tr. (Barnett Cr.) at 617:8-15 (the majority of Dr. Barnett's patients take PPIs, which are "more effective" than an H_2RA), 633:17-20.)

Tolerance issues: In 2007, it was known that PPIs were not associated with tolerance issues, while patients taking H_2RAs were prone to developing tolerance such that efficacy would decline over time, a particularly concerning effect for long-term use during chronic co-administration with NSAIDs. (Tr. (Scheiman Dir.) at 718:16-720:7; DTX 989 at pp. 2, 5; Tr. (Barnett Cr.) at 635:13-641:16; PTX 7-B at p. 1184 ("a degree of tolerance develops during

continued dosing with all available H_2-receptor antagonists," including during administration of 40 mg famotidine daily over the course of 29 days), p. 1187 (gastric acidity levels rising from 225 mmol*h/L on day 1 to 397 mmol*h/L on day 29), p. 1188 (illustrating declining pH levels over time in Figure 1(c)).) This propensity for patient tolerance is attributable to the mechanism of action of H_2RAs as compared to PPIs. (*Id.*; DTX 989 at pp. 2, 5 ("Once effective acid suppression has been achieved with a PPI, it can be maintained over the long term without increasing the dosage. In contrast, tolerance to H_2RAs develops rapidly within 3-5 days of therapy."); Tr. at (Scheiman Dir.) at 712:23-713:4.)

Symptom masking: In 2007, a POSA would have recognized that the prior art explicitly taught *against* the use of H_2RAs to reduce the risk of NSAID-induced GI issues due to concerns that H_2RAs merely masked symptoms, ultimately giving rise to *more* frequent severe adverse effects. (Tr. (Scheiman Dir.) at 721:12-722:13; DTX 114 at pp. 1, 5-6.) As Singh stated:

> DO H_2 ANTAGONISTS … HELP PREVENT SERIOUS GI COMPLICATIONS? … This is a dangerous practice, because these medications may suppress symptoms—potential warning signs—without reducing the risk of serious GI complications. They may provide a false sense of security to both physician and patient, encouraging long-term therapy with higher NSAID doses, which could eventually result in serious GI events. Indeed, the ARAMIS cohort study showed that, of patients who had never had any GI side effects, those who were taking prophylactic GI medications had about 2.5 times ***more*** hospitalizations for NSAID-related GI complications than patients not taking GI medications[.]

(DTX 114 at pp. 5-6 (emphasis added); Tr. (Scheiman Dir.) at 721:12-722:13; DTX 114 at p. 1 ("H_2 antagonists do not prevent NSAID-induced gastric ulcers").)

Alkem argues that rapidity of onset of action, safety, and cost-effectiveness favor an H_2RA over a PPI. (Alk. Op. Br. at 13-15) But these arguments merely restate the reasoning used by Horizon in its investor pitches and ignore that, by 2006, Horizon was actively trying to overcome the concerns in the market regarding "the perceived lack of efficacy on the H_2 receptor

antagonist's ability to reduce ulcers compared to the more … advanced medications, the proton pump inhibitors." (Tr. (Tidmarsh Dir.) at 74:24-75:13 (regarding the use of "strong language" to "convince investors"), 76:17-77:9; Tr. (Tidmarsh Cr.) at 172:25-173:18; DTX 121 at p. 18; *see also* DTX 110 at p. 9.) Alkem's hindsight-driven arguments must be rejected, particularly where, as here, "the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements." *See DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) (warning against "the distortion caused by hindsight bias" and "arguments reliant upon *ex post* reasoning.") (citing *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 36 (1966)).

In any event, in 2007, the time to onset of action would not have mattered to a POSA because it would have been inconsequential during chronic treatment, where the sustained efficacy of PPIs would be preferable. (Tr. (Scheiman Dir.) at 739:24-740:9; Tr. (Gibofsky Dir.) at 205:15-24 (regarding reaching steady-state blood concentrations after several doses of chronic treatments); Tr. (Barnett Dir.) at 598:17-599:5 (suggesting that the rapidity of onset of action would only matter to a POSA assuming that patients are regularly missing or stopping their medications); Tr. (Barnett Cr.) at 629:24-630:14.) In addition, safety was not a concern because there was no association of PPIs with drug interactions or side effects. (Tr. (Scheiman Dir.) at 711:11-712:16, 739:9-23.) And the relative costs of PPIs versus H_2RAs would also not have mattered to a POSA because the efficacy of H_2RAs was in serious doubt. (Tr. (Scheiman Dir.) at 740:10-22.)

c) Taha does not provide a motivation for, or reasonable expectation of success in, using famotidine for reducing the risk of ibuprofen-induced ulcers

Alkem's obviousness case relies heavily on Taha, but a POSA in 2007 would have

recognized the Taha study's numerous limitations, such that a POSA would not have been motivated to use famotidine in combination with ibuprofen with a reasonable expectation of success in reducing the risk of ibuprofen-induced ulceration. (Tr. (Scheiman Dir.) at 724:2-5, 727:2-17; Tr. (Scheiman Cr.) at 748:8-13.)

First, Taha's conclusions are extremely limited as to ibuprofen. In Table 2, Taha reports the incidence of ulcers in each of the patient groups cumulatively, for all NSAIDs studied, rather than on an NSAID-by-NSAID basis. (Tr. (Barnett Cr.) at 623:19-624:8; Tr. (Scheiman Dir.) at 724:2-25; PTX 262 at p. 3.) Moreover, as shown in Table 1, Taha only studied 30 patients taking ibuprofen out of 285 total patients (about 11%). (Tr. (Scheiman Dir.) at 724:2-15, 725:1-21; PTX 262 at p. 2.) The remaining 255 patients took 15 other NSAIDs, including 72 on diclofenac, 53 on indomethacin, and 50 on naproxen. (Tr. (Barnett Cr.) at 621:18-623:18, 624:24-625:5 (affirming that "[i]t would be hard to get statistical significance on any one NSAID" given that the number of patients taking each NSAID is so small); Tr. (Scheiman Dir.) at 724:2-15, 725:1-21; PTX 262 at p. 2.) Accordingly, the Taha study does not support any conclusions or expectations regarding the use of famotidine for reducing the risk of *ibuprofen*-induced ulceration. (Tr. (Scheiman Dir.) at 725:1-5, 725:12-726:5; Tr. (Tidmarsh Cr.) at 162:21-163:5.)

While Alkem suggests that ibuprofen would have been a preferred choice of NSAID based on NSAID toxicity data reported in Singh (DTX 114 at p. 5; Alk. Op. Br. at 13), Singh teaches nothing about the use of famotidine to prevent *ibuprofen*-induced ulcers (Tr. (Scheiman Dir.) at 740:23-741:23), and Singh's findings, like Taha's, encompass a range of undisclosed NSAID doses (even unapproved or over-the-counter doses) and fail to provide any direct comparisons between NSAIDs (Tr. (Barnett Cr.) at 593:23-594:7; DTX 114 at p. 5).

Second, as set forth in Section II.B above, Taha does not disclose the specific dose of

ibuprofen taken. (Tr. (Scheiman Dir.) at 726:6-727:10; PTX 262 at p. 1.) Accordingly, Taha teaches nothing regarding famotidine's efficacy when taken with the specific high dose of ibuprofen of 800 mg TID (2400 mg total daily). (Tr. (Scheiman Dir.) at 726:6-727:10; PTX 262 at p. 1; *see* DTX 281 at p. 11 ("suggested dosage[s]" of ibuprofen as low as 1200 mg daily).)

Third, the Taha study is critically flawed because it uses a "convenience" population of patients who displayed risk factors for ulceration—most notably, that *half* of the patients studied were infected with *H. pylori*. (Tr. (Scheiman Dir.) at 724:2-15; Tr. (Barnett Cr.) at 601:20-24 (regarding Taha's use of "real world patients," e.g., those with a history of ulceration, the use of aspirin, *H. pylori* infection, and/or smoking habits), 627:10-21.) It was understood in 2007 that famotidine could treat or prevent the reoccurrence of *H. pylori*-induced ulcers (Tr. (Barnett Cr.) at 627:16-21; Tr. (Scheiman Dir.) at 697:2-7), and, as set forth in Section II.C.1.a above, that *H. pylori* infection was one of the most common causes of gastric and duodenal ulceration, such that a credible study of famotidine for the prevention of NSAID-induced ulcers would need to exclude *H. pylori* infected patients. A finding that famotidine reduces the incidence of ulcers *in patients taking* NSAIDs (i.e., including ulcers caused by *H. pylori*) is different than a finding that famotidine reduces the incidence of *NSAID-induced* ulcers. Taha is a study of the former and not the latter, such that a POSA could not determine whether famotidine reduced the incidence of NSAID-induced ulcers or simply prevented *H. pylori* ulcers. (Tr. (Scheiman Dir.) at 723:18-724:15, 724:8-15, 729:10-18.)

These limitations of Taha are perhaps why it took nearly 15 years after Taha for DUEXIS® to become the first FDA-approved combination ibuprofen and famotidine product, and the first famotidine product approved to reduce the risk of NSAID-induced ulcers. (Tr. (Scheiman Dir.) at 704:5-8, 727:11-24; Tr. (Barnett Cr.) at 634:12-23.). As well, the limitations

of Taha are in part why, in 2005 and 2006, during the approval process for DUEXIS®, the FDA rejected the suggestion that Taha had demonstrated famotidine's efficacy for reducing the risk of NSAID-induced ulcers. (PTX 707-B at pp. 6-7; Tr. (Tidmarsh Dir.) at 69:3-70:14; *see also* Tr. (Tidmarsh Dir.) at 56:6-57:2, 58:16-59:8, 60:21-62:18; PTX 707-A at p. 2; *see* PTX 763 at pp. 4-5, 15 (citing Taha and "Rostom" (PTX 492)); Tr. (Scheiman Cr.) at 746:25-748:1 ("The Rostom data is basically repeating the Taha study[,]" as it is "a collection of existing literature[,]" which doesn't "analyze the general liability for the patient populations").)

Alkem attempts to discredit Dr. Scheiman, who is one of the preeminent clinicians and researchers in the field of NSAID-induced GI issues (Tr. (Scheiman Dir.) at 695:10-700:8; PTX 322), by cherry-picking statements from one of his numerous publications that discuss Taha (*see* Alk. Op. Br. at 16, 18; Tr. (Scheiman Cr.) at 749:1-750:8; DTX 928 at p. 10). But as the record evidence shows, Dr. Scheiman *did* point out Taha's limitations in 2005, noting that Taha was just a "single study," and that despite the reported findings, "H2 receptor antagonists are not recommended" because of "their potential to mask dyspeptic symptoms associated with mucosal injury" and because they "are less effective in healing gastroduodenal ulcers than are PPIs…." (PTX 496 at p. 3; *see also* PTX 500 at p. 6 (again, noting that Taha is "a ***single study*** demonstrating that H_2RAs at double the dose ***might*** be effective"); Tr. (Scheiman Dir.) at 727:25-729:18 (noting that efficacy for preventing ulcers "in patients taking NSAIDs" is different than efficacy for preventing "NSAID-induced ulcers").)

Alkem points to Horizon's reliance on Taha in documents submitted to the FDA and investors as being supportive of obviousness (Alk. Op. Br. at 17-18), but Alkem overlooks the purpose for which Horizon cited Taha in those documents (Tr. (Tidmarsh Dir.) at 58:6-15 (Taha was "a single study which supported our hypothesis" but which had not proven that famotidine

TID could prevent ibuprofen-induced ulcers), 74:24-75:13 (regarding the use of "strong language" to "convince investors"); Tr. (Tidmarsh Cr.) at 156:20-157:2, 160:22-161:4; DTX 121 at p. 16; DTX 110 at pp. 3, 6).

In any event, another publication in 1999, Wolfe, plainly stated the view that, despite Taha, "the use of H2-receptor antagonists for the prevention of NSAID-associated ulcers cannot be recommended[.]" (Tr. (Scheiman Dir.) at 734:1-21; PTX 531 at 8 (also teaching that "proton-pump inhibitors are superior to H_2-receptor antagonists").)

Taha, at best, presented a hypothesis that warranted further evaluation. (Tr. (Scheiman Dir.) at 724:2-5, 725:1-5, 725:22-726:5, 727:2-17.) But a hypothesis is not enough to provide a reasonable expectation of success. *See Pfizer Inc. v. Watson Pharms., Inc.*, 920 F. Supp. 2d 552, 563 (D. Del. 2013) (Andrews, J.) ("Patents are not barred just because it was obvious to explore a new technology or general approach that seemed to be a promising field of experimentation."); *Genzyme Corp. v. Dr. Reddy's Labs., Ltd.*, No. 13-1506-GMS, 2016 WL 2757689, at *12 (D. Del. May 11, 2016) (no showing of obviousness based on "hope" as to clinical results, rather than an "expectation"); *Sanofi v. Glenmark Pharm. Inc., USA,* 204 F. Supp. 3d 665, 696 (D. Del. 2016) (Andrews, J.) (no reasonable expectation of success where POSA "would have been at best cautiously optimistic that [the drug at issue] could [produce the desired effect,]" which a reference stated was "expected" based on a post-hoc analysis, thereby merely "provid[ing] a hypothesis … for a POSA to test through further experimentation").

2. A POSA would not have been motivated to dose, or have a reasonable expectation of success in dosing, 26.6 mg famotidine TID for reducing the risk of ibuprofen-induced ulceration

A POSA would not have been motivated to administer 26.6 mg of famotidine TID with any reasonable expectation of success that it would be effective to reduce the risk of ibuprofen-induced ulceration. First, in 2007, neither a 26.6 mg dose nor a TID dosing regimen of

famotidine was approved by the FDA for any purpose. (Tr. (Scheiman Dir.) at 735:1-14; Tr. (Barnett Cr.) at 614:9-617:1, 617:18-618:10, 620:5-23; DTX 120 at pp. 8-9.) A POSA therefore could not have extrapolated the untested pharmacokinetics and pharmacodynamics of 26.6 mg famotidine TID to this unproven prophylactic use. (Tr. (Scheiman Dir.) at 735:1-736:7.) And a POSA would not have expected that any efficacy associated with a 40 mg dose of famotidine given BID, as allegedly reported by Taha, could be extrapolated to a 26.6 mg dose of famotidine given TID. (Tr. (Scheiman Dir.) at 735:7-736:7.) A POSA would have recognized that, at best, any hypothesis that one could simply divide an 80 mg total daily dose into TID dosing rather than BID dosing needed to be tested before forming the basis for any expectations of success. (*Id.*; *see* Tr. (Tidmarsh Dir.) at 53:25-54:15, 75:14-76:10; Tr. (Tidmarsh Cr.) at 162:1-14.)

Second, the '096 publication would not have offered a POSA any reasonable expectation of success in using 26.6 mg famotidine TID to reduce the risk of ibuprofen-induced ulceration. (Tr. (Scheiman Dir.) at 738:24-739:8.) The evidence supporting the use of TID dosing in the '096 publication is limited to a single pharmacokinetic model in Example 1, which studied the differences in gastric pH resulting from TID versus BID famotidine dosing regimens, and specifically, the length of time that gastric pH remained greater than 3.5. (Tr. (Scheiman Dir.) at 736:8-24; PTX 371 at pp. 19-20, ¶¶ [0179]-[0182].) But the study did not consider the concomitant use of ibuprofen, and, as set forth in Section II.C.1.a above, there was no understanding in 2007 that maintaining a gastric pH above a certain value for any particular length of time would actually translate to clinical efficacy for reducing the incidence of NSAID-induced ulcers. (Tr. (Scheiman Dir.) at 709:25-710:10, 736:25-737:7; Tr. (Tidmarsh Dir.) at 91:15-18, 92:5-14 ("stomach acid contributes to the GI toxicity but it doesn't allow us to conclude efficacy about the reduction in the ulcers"); PTX 371 at ¶¶ [0179]-[0182].) Moreover, a

POSA would not have expected that this computer-simulation could accurately predict the effects of famotidine on gastric pH levels in human patients. (Tr. (Scheiman Dir.) at 737:11-20; Tr. (Scheiman Cr.) at 745:2-5; PTX 371 at ¶ [0179] (results "can be confirmed in clinical trials and may deviate somewhat from the predicted values[.]").) The results in Example 1 were also modeled from data taken from just *one* individual, such that the results would have been of questionable value in driving any expectations regarding a target *population* of patients. (Tr. (Scheiman Dir.) at 737:21-738:10; Tr. (Tidmarsh Dir.) at 91:19-92:4; PTX 371 at ¶ [0181].)

Additionally, while the '096 publication also discloses an *anticipated* clinical study of famotidine dosed TID versus BID in Example 2, only aspirational expectations, rather than any actual results, were provided, and even so, the expectations relate solely to effect on gastric pH rather to efficacy to reduce risk of ibuprofen-induced ulcers. (Tr. (Scheiman Dir.) at 738:11-739:1; Tr. (Scheiman Cr.) at 745:6-10; Tr. (Tidmarsh Dir.) at 92:15-93:15; PTX 371 at pp. 20-21, ¶¶ [0183]-[0190], [0191] ("It is expected that …").) *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070 (Fed. Cir. 2012) ("While it may have been obvious to experiment with the use of the same PK profile …, there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective.").)

Finally, Alkem cites Echizen and Edge (Alkem Op. Br. at p. 5), but neither Echizen nor Edge bears any relation to the use of famotidine for reducing the risk of NSAID-induced ulcers. Echizen discusses the pharmaco*kinetics*—not the pharmaco*dynamics*—of famotidine, and it acknowledges that "little information is available on its pharmaco*kinetic* behavior during multiple-dose administration," and that "further studies are definitely required to assess its more detailed pharmaco*kinetic* characteristics during multiple-dose administration." (Tr. (Scheiman

Dir.) at 741:24-742:20; DTX 772 at pp. 7-8 (emphasis added).) Echizen says nothing about reducing the risk of NSAID-induced ulcers, an unproven pharmaco*dynamic* effect of famotidine. (Tr. (Scheiman Dir.) at 742:17-20; *see also* DTX 772 at p. 12 (mentioning only healing active ulcers).) Similarly, Edge studied famotidine to treat esophagitis, which is not a gastric or duodenal condition, and the patients undergoing treatment were instructed to stop taking NSAIDs as part of the study, meaning that Edge teaches a POSA nothing about the use of famotidine for reducing the risk of NSAID-induced ulcers. (Tr. (Barnett Cr.) at 618:11-619:22; Tr. (Scheiman Dir.) at 742:21-743:20; DTX 749 at pp. 1-2.) Accordingly, neither Echizen nor Edge renders the claims obviousness. *See*, *e.g.*, *Bausch Health Cos. Inc. v. Actavis Labs. FL, Inc.*, No. CV 16-9038 (SRC), 2019 WL 3214550, at *24 (D.N.J. July 17, 2019) (rejecting expert's testimony which "simply selects and combines various teachings drawn from the prior art" as "conclusory" and "a hindsight-driven attempt to escape the obligation to show the motivation to select and combine its components").

3. A POSA would not have been motivated to select ibuprofen and famotidine for use in a combination product due to their extreme incompatibility

Alkem alleges that a POSA would have been motivated to develop a product that was "stable for the expected shelf-life," including, "typically 3-5 years[.]" (Alk. Op. Br. at 18-19.) Yet, Alkem ignores the clear teaching in the '096 publication, as set forth below, that ibuprofen and famotidine were extremely incompatible with one another, with ibuprofen causing the rapid and extensive degradation of famotidine in short order under forced degradation conditions.[5] Accordingly, as the evidence of record supports, if a POSA were motivated to formulate a

[5] Although the '096 publication is not available as prior art, its teachings are still relevant to both motivation and reasonable expectation of success. *See, e.g.*, *Nat'l Steel Car, Ltd. v. Canadian Pac. Ry., Ltd.*, 357 F.3d 1319, 1337–38 (Fed. Cir. 2004); *AstraZeneca LP v. Breath Ltd.*, 88 F. Supp. 3d 326, 350 (D.N.J. 2015).

dosage form that was "stable for the expected shelf-life of the drug product," as Alkem alleges, then the POSA would *not* have been motivated to combine 800 mg ibuprofen and 26.6 mg famotidine into a single unit dosage form. (Tr. (Little Dir.) at 754:21-755:13.)

Example 4 of the '096 publication sets forth three ibuprofen and famotidine compatibility studies that illustrate their extreme incompatibility under forced degradation conditions. (Tr. (Little Dir.) at 754:21-755:19; PTX 371 at pp. 12-13, ¶ [0083], p. 22, ¶¶ [0205]-[0207] (Tables 4-6).) Table 4 sets forth stability data for mixtures of famotidine and ibuprofen in a ratio of 1 to 29, essentially the same ratio of famotidine to ibuprofen recited in claim 1 of the '033 patent, which show that, at elevated temperatures, famotidine alone is stable, but when mixed with ibuprofen, famotidine degrades rapidly (i.e., by 19% when stored for two weeks at 60° C and by 46% when stored for one month at 40° C and 75% relative humidity). (Tr. (Little Dir.) at 755:14-756:18; PTX 371 at ¶ [0205].) Table 5 sets forth similar stability data, this time for 400 mg ibuprofen and 13.3 mg famotidine, the same ratio of famotidine to ibuprofen recited in claim 1 of the '033 patent, in an admixture single layer tablet, which show that the famotidine degraded rapidly (i.e., by 61% when stored for one week at 60° C and by 17% when stored for one month at 40° C and 75% relative humidity). (Tr. (Little Dir.) at 756:23-757:23; PTX 371 at ¶ [0206].) Table 6 sets forth additional stability data for tablets containing 400 mg ibuprofen and 10 mg famotidine, which shows that 99% famotidine remained after storage at room temperature for four months, but famotidine degraded almost entirely, with only 4% remaining, after storage at 60° C for one month. (Tr. (Little Dir.) at 757:24-758:7; PTX 371 at ¶ [0207].)

Based on these teachings of the '096 publication, a POSA would understand that ibuprofen will rapidly and extensively degrade famotidine when in a combination tablet under forced degradation conditions. And the POSA would not have chosen ibuprofen in combination

with famotidine, especially in dosage amounts of 800 mg and 26.6 mg, respectively, as the data in the '096 publication show that famotidine will rapidly and extensively degrade when present with ibuprofen in a ratio of 1 to 30.

4. A POSA would not have had a reasonable expectation of success in combining 800 mg ibuprofen and 26.6 mg famotidine to achieve the level of stability required by claims 1 and 14 of the '033 patent

Claims 1 and 14 of the '033 patent require that the claimed pharmaceutical composition contain (1) no more than about 1% sulfamide when stored at 40° C and 75% relative humidity for one month (*see* claim 1) and (2) at least 98% ibuprofen and at least 98% famotidine when stored at room temperature conditions of 25° C and 60% relative humidity for nine months (*see* claim 14). Alkem cites to the USP NF (PTX 559) as support that a POSA would have been motivated to develop a pharmaceutical product that meets the claimed level of stability (Alk. Op. Br. at 23, 27), and Alkem cites to either the '671 publication (DTX 136) or the '876 publication (DTX 785) as support that the claimed level of stability could be achieved through the routine optimization of the dosage forms used therein (Alk. Op. Br. at 24, 27, 30). However, as set forth below, the USP NF only offers a POSA an "aspirational goal" for stability—not a reasonable expectation of success that such goal could actually be achieved. And neither the '671 publication nor the '876 publication includes sufficient information for a POSA to have had any reasonable expectation of success that utilizing their dosage form designs would achieve the high level of stability required by claims 1 and 14.

a) The impurity standards in the USP NF present nothing more than an "aspirational goal"

While a POSA may have viewed the impurity standards set forth in the USP NF for ibuprofen tablets and famotidine tablets as an "aspirational goal" for a combination product containing both ibuprofen and famotidine, the evidence presented at trial supports that the POSA

could not have had any reasonable expectation of success that those standards were actually achievable. First, Alkem ignores that the USP does not contain *any* teaching that at least 98% ibuprofen and at least 98% famotidine should be present after storage at room temperature conditions of 25° C and 60% relative humidity for nine months. Instead, the USP NF directs a POSA to much lower amounts of each active ingredient, stating only that not less than 90.0% of each active ingredient should be present. (Tr. (Chambliss Cr.) at 559:22-561:4; PTX 559 at pp. 8-9, 12-13.)

Second, it is improper hindsight to assume that a POSA would have been able to formulate a combination product that contains 800 mg ibuprofen and 26.6 mg famotidine and that meets the impurity standards set forth in the USP NF. The standards set forth in the USP NF are for famotidine tablets that do not contain ibuprofen, and ibuprofen tablets that do not contain famotidine, wherein both individual tablets have already been successfully formulated and approved for sale by the FDA. (Tr. (Little Dir.) at 763:22-764:19; PTX 559 at pp. 8-9, 12-13.). A POSA would understand that while such impurity standards may be achievable for individual tablets of each active ingredient, the POSA would *not* understand that those same impurity standards may be achievable for a combination product that contains *both* active ingredients. (Tr. (Little Dir.) at 763:22-765:19; Tr. (Little Cr.) at 794:18-795:13.) This is particularly true here, where the POSA would understand that ibuprofen and famotidine are extremely incompatible with one another under forced degradation conditions. (*See* Section II.C.3, *supra*.) Importantly, it is impermissible hindsight for Alkem to simply point to the stability result that the inventors were able to achieve as support that this result would have been reasonably expected by a POSA.

b) The ’671 publication does not provide a reasonable expectation of success

The ’671 publication would not offer a POSA a reasonable expectation of success that the

high level of stability required by the asserted claims could be achieved given the very limited information set forth in the '671 publication concerning the degree of instability that was overcome and the level of stability that was ultimately achieved. (Tr. (Little Dir.) at 767:6-769:24; Tr. (Little Cr.) at 800:23-801:4, 811:8-17; Tr. (Chambliss Cr.) at 550:3-7; DTX 136 at p. 2, ¶¶ [0004]-[0005], pp. 4-6, ¶¶ [0036]-[0065].)

The '671 publication is directed to formulating two different active ingredients, ranitidine and acetylsalicylic acid, or aspirin. And while the '671 publication includes a conclusory statement that the dosage form designs disclosed therein overcome the incompatibility of these two active ingredients, the '671 publication does not describe which active ingredient is degrading the other (Tr. (Little Dir.) at 769:25-770:18; Tr. (Chambliss Cr.) at 550:23-551:16), the degradants that are formed as a result of the incompatibility of ranitidine and aspirin (Tr. (Chambliss Cr.) at 551:17-20), or the mechanism of degradation that is occurring (Tr. (Little Dir.) at 769:25-770:18; Tr. (Chambliss Cr.) at 550:8-22). Additionally, the '671 publication does not contain any stability data, providing a merely qualitative statement that ranitidine remained stable for six months and ibuprofen remained stable for two months at 40° C and 75% relative humidity. (Tr. (Little Dir.) at 768:25-769:24; DTX 136 at p. 6, ¶¶ [0060], [0065].)

Alkem and Dr. Chambliss seize on this conclusory statement regarding stability, but the '671 publication provides no explanation as to what is meant by "stable" (Tr. (Little Dir.) at 769:16-24; Tr. (Little Cr.) at 806:18-807:16, 811:8-17; DTX 136 at p. 6, ¶¶ [0060], [0065]), and the '671 publication does not include the percentage of degradants that were formed or the percentage of each active ingredient that remained after storage under forced degradation conditions (Tr. (Little Cr.) at 801:5-18; Tr. (Chambliss Cr.) at 552:5-7). The '671 publication also does not provide any comparative stability data that shows just how incompatible ranitidine

and aspirin are when in an admixture or multiparticulate dosage form. (Tr. (Little Dir.) at 767:24-768:3, 770:19-771:1; Tr. (Little Cr.) at 796:15-23, 797:11-798:6, 799:24-800:4, 801:5-18, 806:18-22, 811:8-17.) Accordingly, a POSA would not have any understanding as to the actual level of stability that was achieved by, or the degree of instability that was overcome by, using the dosage form design set forth in the '671 publication. And, thus, a POSA would not know whether the formulation strategy used in the '671 publication could solve the extreme incompatibility of ibuprofen and famotidine to the degree and extent required by the level of stability set forth in claims 1 and 14 of the '033 patent. (Tr. (Little Cr.) at 809:7-16.)

c) The '876 publication does not provide a reasonable expectation of success

Similarly, the '876 publication would not offer a POSA a reasonable expectation of success that the high level of stability required by the asserted claims could be achieved because the '876 publication is not directed to solving the incompatibility of two active ingredients, let alone two active ingredients that are as incompatible as ibuprofen and famotidine. (Tr. (Little Dir.) at 772:19-773:24, 777:6-9, 778:12-19; Tr. (Chambliss Cr.) at 558:21-559:4, 559:16-19.) Rather, the '876 publication is directed to formulating an acid labile active ingredient that passes through the stomach to release in the small intestine where the pH is higher. (Tr. (Little Dir.) at 773:3-10, 774:18-775:19; DTX 785 at pp. 4-5, ¶¶ [0028], [0036]-[0038].) A POSA would not find the '876 publication relevant to overcoming the incompatibility of two active ingredients or as providing any reasonable expectation of success that the dosage form designs of the '876 publication would be sufficient to solve an incompatibility issue.

Additionally, even if a POSA did look to the '876 publication for guidance, the POSA would not arrive at the claimed immediate release product containing ibuprofen and famotidine. The '876 publication is not directed to preparation of formulations containing two active

ingredients for immediate release. (Tr. (Little Dir.) at 773:11-18, 774:18-775:19; Tr. (Chambliss Cr.) at 558:10-14; DTX 785 at p. 5, ¶¶ [0033], [0035]-[0038].) Rather, the '876 publication is directed to coordinated release dosage forms, wherein one active ingredient is immediately released while the other active ingredient is formulated for sustained release. (Tr. (Little Dir.) at 773:11-18, 774:18-775:19, 778:19-22; DTX 785 at p. 5, ¶¶ [0033], [0035]-[0038].)

A POSA would not have been motivated to use famotidine in place of the acid labile active ingredient. (Tr. (Little Dir.) at 776:17-777:5.) The '876 publication defines an acid labile active ingredient as one that must be specially formulated to pass through the stomach unharmed and then released into the intestinal tract. (Tr. (Little Dir.) at 775:20-776:8; DTX 785 at p. 3, ¶ [0002].) The '876 publication does not describe famotidine as an acid labile active ingredient, and a POSA would not understand famotidine to be an acid labile active ingredient because, as Dr. Chambliss openly touts, famotidine can be released safely into the stomach. (Tr. (Little Dir.) at 776:9-777:5; Tr. (Chambliss Dir.) at 554:8-15; DTX 785 at pp. 5-6, ¶ [0044].)

Finally, the '876 publication does not disclose a dosage form that contains both ibuprofen and famotidine. (Tr. (Little Dir.) at 777:18-21; Tr. (Chambliss Cr.) at 556:20-24.) Rather, the '876 publication describes both ibuprofen and famotidine as optional second active ingredients. (Tr. (Little Dir.) at 777:10-17; Tr. (Chambliss Cr.) at 554:16-556:13; DTX 785 at pp. 5, 9-10, ¶¶ [0043], [0085]-[0090].)

d) The '696 patent supports the lack of a reasonable expectation of success in achieving the claimed levels of stability

The unrebutted evidence of record shows that a POSA would not have had a reasonable expectation of success in achieving the claimed level of stability when formulating two incompatible active ingredients in view of the '696 patent. The '696 patent relates to improving the stability of compositions containing famotidine and sucralfate, where sucralfate is known to

degrade famotidine, by coating famotidine particles with a barrier layer. (Tr. (Little Dir.) at 779:11-780:9; PTX 376 at 1:53-56, 1:68-2:3.) Unlike the '671 publication and the '876 publication relied upon by Alkem, the '696 patent actually contains stability data, which show that simply separating two active ingredients into compartments does not necessarily achieve the level of stability required by claims 1 and 14, contrary to Alkem's assertions of mere routine optimization. (Tr. (Little Dir.) at 780:10-11.)

In the '696 patent, eight dosage forms were studied, where samples 1, 2, A, and B were bilayer, compartmentalized tablets, and samples 3, 4, C, and D were multiparticulate, single layer tablets. (Tr. (Little Dir.) at 780:12-781:1; PTX 376 at 4:65-5:5, 5:12-14.) Additionally, samples 1, 2, 3, and 4 contained a barrier layer on the famotidine, while samples A, B, C, and D did not contain any barrier layer material. (Tr. (Little Dir.) at 780:20-22; PTX 376 at 4:65-5:5.) These eight samples were placed on stability for 5 weeks at 40° C and 75% relative humidity.

A comparison of the resulting stability data for sample 2 in contrast to samples 3 and 4 supports a lack of reasonable expectation of success. Sample 2 used a compartmentalized dosage form with a barrier layer but still had 2.50% total degradates, while samples 3 and 4 were prepared as *non-compartmentalized* multiparticulate dosage forms but had a *lower* amount of total degradates, i.e., 0.19% and 0.28%, respectively. (Tr. (Little Dir.) at 781:22-782:22; PTX 376 at Table 1.) These stability data support that a POSA would not reasonably expect that simply separating two incompatible active ingredients into compartments, either with or without a barrier layer, would be sufficient to achieve the level of stability required by the Asserted Claims. (*Id.*) *See Novartis Pharms. Corp. v. Noven Pharms., Inc.*, 125 F. Supp. 3d 474, 482 (D. Del. 2015) (Andrews, J.) (no reasonable expectation of success where "actual testing [was] necessary" to determine chemical instability of claimed compound).

III. THE ASSERTED CLAIMS OF THE '033 PATENT ARE DEFINITE

Alkem cannot meet its burden of proving that the claim term "sulfamide" is indefinite by clear and convincing evidence. *See BASF Corp. v. Johnson Matthey Inc.*, 875 F.3d 1360, 1365 (Fed. Cir. 2017). Alkem's theory of indefiniteness is directly contradicted by the testimony of Alkem's expert, Dr. Laird, whose testimony is fully supportive of what Alkem characterizes as Horizon's "trail of breadcrumbs and assumptions" (Alk. Op. Br. at 33). Based on the record evidence, there can be no doubt that a POSA would conclude "with reasonable certainty" that the claim term "sulfamide" refers to Famotidine Impurity C in the USP (PTX 559). *See Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014).

A. Dr. Laird's testimony supports that a POSA would understand "sulfamide" to mean Famotidine Impurity C in the USP with reasonable certainty

As set forth in Horizon's Opening Brief (D.I. 218, "Hzn. Op. Br."), a POSA would have understood that, depending on context, the term "sulfamide" can either refer to the small molecule sulfamide or a larger molecule that contains a sulfamide functional group. (*Id.* at 18.) Notably, this is not in dispute, as Alkem's own expert, Dr. Laird, provided this exact testimony. (Tr. (Laird Dir.) at 659:10-15.) Additionally, as Alkem agrees, the '033 patent explains that "sulfamide" is "a principal degradant of famotidine formed by the interaction of famotidine and ibuprofen." (Alk. Op. Br. at 31.) And as set forth in Horizon's Opening Brief, a POSA would have understood that "sulfamide" in the '033 patent does not refer to the small molecule sulfamide, but instead means Famotidine Impurity C in the USP because it is the only known principal degradant that contains a sulfamide functional group and that is formed as a result of the acid-catalyzed hydrolysis of famotidine. (Hzn. Op. Br. at 19.)

There can be no reasonable dispute on this point, as Dr. Laird has agreed that (1) "sulfamide" was a known famotidine degradant set forth in the literature in 2007, produced as

a result of the ibuprofen molecule degrading the famotidine molecule (Tr. (Laird Cr.) at 685:13-686:2, 686:8-687:6); (2) famotidine is susceptible to acid catalyzed hydrolysis to form Famotidine Impurity C, which is the mechanism by which ibuprofen will degrade famotidine (Tr. (Laird Cr.) at 687:7-688:1, 691:8-11); (3) a POSA would consult the USP monograph, "the definitive publication … about impurities," for famotidine tablets, to determine the meaning of "sulfamide" (Tr. (Laird Cr.) at 688:2-14; *see also* Tr. (Laird Dir.) at 663:22-664:1, 664:9-15); (4) a POSA would not understand the term "sulfamide" to refer to Famotidine Impurities B or D in the USP because neither contains a sulfamide functional group (Tr. (Laird Cr.) at 689:4-690:3, 690:22-24); and (5) Impurity A is not the result of the acid catalyzed hydrolysis of famotidine and will not form as a result of ibuprofen degrading famotidine (Tr. (Laird Cr.) at 690:12-21). Thus, based solely on the information contained in the '033 patent, together with a POSA's knowledge and the USP, there can be only one reasonable conclusion—that the claim term "sulfamide" refers to Famotidine Impurity C. (*See* Hzn. Op. Br. at 18-21.)

Alkem's attempt to analogize this case to *HZNP Medicines LLC v. Actavis Labs. UT, Inc.*, 940 F.3d 680 (Fed. Cir. 2019), fails. (Alk. Op. Br. at 30-31.) While it is true that in *HZNP Medicines*, the Federal Circuit affirmed the district court's finding that the claim term "impurity A" was indefinite because the claims did not make clear that "impurity A" referred to an impurity of diclofenac sodium, the facts are very different. In *HZNP Medicines*, the court found there was a discrepancy in relative retention times for "impurity A" in the United States and European Pharmacopeia, such that without a clear HPLC method included in the patent specification, a POSA would be unable to ascertain what was meant by "impurity A." 940 F.3d at 690-691; *see also Horizon Pharma Ireland Ltd. v. Actavis Labs., UT, Inc.*, C.A. No. 14-7992, 2016 WL 4408990, at *3-*4 (D.N.J. Aug. 17, 2016). There is no such discrepancy here. All the

prior art literature supports that the famotidine degradant that is produced as a result of the acid catalyzed hydrolysis of famotidine is Famotidine Impurity C. (*See* Hzn. Op. Br. at 20-21.)

B. Alkem's indefiniteness theories are directly contradicted by Dr. Laird's testimony and the evidence of record

Alkem argues that "sulfamide" might refer to the small molecule sulfamide, rather than a larger molecule that contains a sulfamide functional group, and points to Junnarkar and Yanagisawa, which refer to Famotidine Impurity C as "sulfamoyl amide," rather than "sulfamide." (Alk. Op. Br. at 32-34.) But as discussed in Horizon's Opening Brief, Junnarkar identifies the small sulfamide molecule as a *byproduct* of famotidine degradation, and Yanagisawa includes the small sulfamide molecule as a *reagent* in a chemical reaction—not as a famotidine degradant itself. (Hzn. Op. Br. at 20; PTX 442 at p. 3; PTX 535 at p. 4 (Scheme II).) Additionally, a POSA would understand that the small sulfamide molecule has a mass that is about one fifth the mass of any one of the famotidine related compounds or impurities set forth in the USP. (Tr. (Little Dir.) at 783:23-785:17; Tr. (Laird Cr.) at 691:12-692:7.) Thus, the small molecule sulfamide would not even be measurable by any method of detection, in comparison to the significantly larger famotidine related compounds or impurities in the USP, such that a POSA would not understand the small sulfamide molecule to be a degradant of famotidine, let alone the *principal* degradant, as defined by the '033 patent. Additionally, as set forth in Horizon's Opening Brief, Dr. Little testified, and Dr. Laird agreed, that "sulfamide" and "sulfamoyl amide" refer to the same portion of the Famotidine Impurity C molecule. (Tr. (Little Dir.) at 296:1-16; Tr. (Laird Cr.) at 690:22-691:7.)

Next, Alkem argues that "sulfamide" does not need to be formed by the acid catalyzed hydrolysis of famotidine, and that "sulfamide" may refer to Famotidine Impurity A. (Alk. Op. Br. at 33, 34.) Alkem's theory is entirely inconsistent with the record evidence, including

admissions made by Dr. Laird. Dr. Laird agreed that, based on the information contained in the '033 patent, a POSA would understand that "sulfamide" is produced as a result of *the ibuprofen molecule* degrading the famotidine molecule (Tr. (Laird Cr.) at 685:13-686:2)—not that ibuprofen can first become oxidized, and then *the oxidation products of ibuprofen* react with famotidine to produce "sulfamide" (Tr. (Little Dir.) at 293:20-294:16). Moreover, while the '033 patent does not explicitly state that ibuprofen degrades famotidine according to an acid catalyzed hydrolysis reaction, Dr. Laird agreed that this is the mechanism by which ibuprofen will degrade famotidine, and that Famotidine Impurity C is produced as a result of the acid catalyzed hydrolysis of famotidine. (Tr. (Laird Cr.) at 687:11-16, 687:21-688:1, 691:8-11.)

Finally, Alkem confusingly argues that the term "sulfamide" need not refer to a molecule containing a sulfamide moiety, and that "sulfamide" can refer to Famotidine Impurity B. (Alk. Op. Br. at 33, 34-35.) This position conflicts with the testimony that Alkem elicited from Dr. Laird. Specifically, Dr. Laird was asked, "Other than the sulfamide molecule, would a skilled person have had any other understanding of what the word sulfamide meant by 2007?" In response, Dr. Laird explicitly testified: "Yes. . . .[T]he sulfamide could be – it's a compound with a sulfamide moiety in it." (Tr. (Laird Dir.) at 659:10-15.) For Alkem to now suggest that the term "sulfamide" can refer to a large molecule that does *not* contain a sulfamide moiety would go against all of the evidence in the record.

IV. CONCLUSION

For the foregoing reasons, Horizon respectfully requests that this Court find that claims 1, 8, 11, and 14 of the '033 patent are not invalid, as well as such other and further relief as this Court may deem just and proper.

Respectfully submitted,

Date: October 6, 2020

/s/ Chad S. C. Stover

Chad S.C. Stover (No. 4919)
1000 N. West Street, Suite 1500
Wilmington, Delaware 19801
Telephone: (302) 300-3474
chad.stover@btlaw.com

Of Counsel:

Caryn C. Borg-Breen
Jessica Tyrus Mackay
Timothy J. O'Brien
GREEN GRIFFITH & BORG-BREEN LLP
676 North Michigan Avenue, Suite 3900
Chicago, Illinois 60611
Telephone: (312) 883-8000
cborg-breen@greengriffith.com
jmackay@greengriffith.com
tobrien@greengriffith.com

Attorneys for Plaintiff Horizon Medicines LLC